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Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States)

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Abstract

Objective To evaluate whether maternal use of recreational drugs around conception and pregnancy influences the risk of childhood neuroblastoma.

Methods Self-reported use of recreational drugs from one month prior to pregnancy until diagnosis was assessed among mothers of 538 children with neuroblastoma (diagnosed 1992–1994 and identified through the Children's Cancer Group and Pediatric Oncology Group) and 504 age-matched controls (identified by random-digit dialing). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression, adjusting for age at diagnosis and household income.

Results Maternal use of any illicit or recreational drug around pregnancy was associated with an increased risk of neuroblastoma in offspring (OR = 1.82, 95% CI: 1.13, 3.00), particularly use of marijuana in the first trimester of pregnancy (OR = 4.75, 95% CI: 1.55, 16.48). Marijuana use in the month before pregnancy did not increase risk. The effect of gestational marijuana exposure was strongest in subjects diagnosed before age one. Evaluation of recreational drugs other than marijuana was limited by infrequent use, and analyses of drug use by fathers were not carried out due to missing data.

Conclusions Maternal recreational drug use and marijuana use during pregnancy were associated with increased risk of neuroblastoma in offspring. Further examination of these drugs and the risk of childhood cancer is warranted.

Keywords Neuroblastoma · Marijuana smoking · Case-control studies · Prenatal exposure delayed effects · Maternal exposure

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Introduction

A number of epidemiological studies have examined health effects of recreational or illicit drugs. These substances include marijuana, cocaine, heroin, amphetamines, and stimulants. In a 2002 nationwide in-person survey of American adults aged 18–25 years, 53.8% reported any lifetime use of marijuana, 24.2% reported hallucinogens, 15.4% reported cocaine, and 1.6% reported heroin use [1].

Parental marijuana use has been associated with several childhood malignancies including leukemia [2, 3], brain tumors [4] and rhabdomyosarcoma [5]. Studies have identified modest associations with both maternal [2, 4, 5] and paternal [3] use of marijuana during pregnancy and during the period 1–3 months before conception. Analyses

of other prenatal illicit drugs including cocaine [5] and amphetamines [3] have suggested increased risk of childhood cancer.

Neuroblastoma is the most common extracranial solid tumor of childhood, with a poorly understood environmental and genetic etiology. The diagnosis is most frequent in infants and very young children, with a mean age at diagnosis of 17.3 months [6]. The early age at diagnosis has prompted investigations of environmental exposures around the time of conception and during pregnancy [7]. Drugs inconsistently found to be associated with neuroblastoma when used by pregnant women include diuretics [8], alcohol [8], analgesics and pain relievers [9], opioid agonists [10], and other medications [8]. No study has examined the role of illicit drugs in the etiology of neuroblastoma. The current analysis, based on a large case-control study of neuroblastoma, evaluated the timing and intensity of maternal prenatal marijuana and four other classes of recreational drugs: cocaine, heroin, hallucinogens, and stimulants.

Subjects and methods

Cases were identified at 139 North American treating hospitals in the Children's Cancer Group and Pediatric Oncology Group, now merged into the Children's Oncology Group. To be eligible, case children must have received a new diagnosis of neuroblastoma from May 1992 to April 1994 between birth and age 19 years. Additional requirements for eligibility included physician consent, parental consent, a household telephone, and biological mother's availability for interview and English- or Spanish-language proficiency. Additional study details have been described previously [11]. The study was approved by the institutional review board regulating human subject research at each participating institution. Of 741 eligible cases identified, 538 mothers (73%) were interviewed.

Controls were selected by random-digit dialing, matched by age within 6 months for cases aged 3 years or younger and within 1 year for cases older than 3 years. Of 703 eligible control mothers, 504 (72%) were interviewed. The maternal interview was conducted by trained interviewers using a standardized questionnaire and lasted approximately 1 h. In addition to demographics, information was requested on the child's environmental exposures up to the case age at diagnosis (the reference date for cases and controls), and on antenatal parental exposures including occupational exposures. Parents were questioned about tobacco smoking and alcohol use and about use of any recreational substances. In a separate interview section, mothers of cases and controls were asked about any use of marijuana between the month prior to pregnancy and the

child's date of diagnosis or reference date. Mothers were specifically asked to quantify the amount and frequency of their use in terms of the usual number of reefers or pipefuls smoked in 1 day during each of the following time segments: the month before pregnancy, each of three trimesters, and between birth and the reference date. If applicable, use was also assessed from the time while breastfeeding up until the reference date. Mothers were also asked about any use of cocaine or crack; heroin; hallucinogens ''such as LSD, PCP, and angel dust''; or stimulants ''such as uppers, amphetamines, and speed.'' For each drug category, detailed questions were asked to establish the frequency and duration of use during each of the following time segments: 2–12 months before pregnancy, the month before pregnancy, each trimester, and, if applicable, from the time during breastfeeding up until diagnosis or reference date.

The odds ratio (OR) and 95% confidence interval (CI) were estimated using unconditional logistic regression. We evaluated maternal use of each of five classes of illicit drugs by ever/never use during a 10-month interval of interest extending from the month prior to conception until childbirth. We also evaluated use of each class of drugs during pregnancy, excluding the month before conception. We evaluated maternal use of marijuana by specific time segment, including the month before conception and each trimester of pregnancy. We assessed infrequent (<1/day) versus regular (≥1/day) intensity of marijuana use and total number of uses around pregnancy. There were insufficient reports of other drugs to further characterize their effects at different time segments or by intensity. The referent category for each class of drug was mothers who did not use that drug at any time reported in the interview. Subjects were excluded from specific analyses if data on use of that drug were missing. Because of the focus on likely critical exposure windows around conception and during pregnancy, we did not analyze recreational drug use between the end of breastfeeding and the date of diagnosis or reference date.

Potentially confounding factors included: child's gender, maternal age at birth of index child, maternal attained education, household income, maternal race, vitamin use, breastfeeding, maternal smoking, and maternal alcohol use. Both maternal prenatal multivitamin use and breastfeeding were associated with a reduced risk of neuroblastoma, as we have previously reported [12, 13]. Maternal cigarette smoking and alcohol use during pregnancy were not found to be associated with the risk of neuroblastoma, as has been previously published [14]. Only household income in the year of child's birth exceeded a 10% change in value estimate using a backward elimination modeling approach and was therefore adjusted for in the analysis. All odds ratio estimates were adjusted for household income and for child's reference age (the matching factor) in three

categories (< 1 year, 1–3 years, >3 years). We assessed the heterogeneity of the maternal marijuana use effect by child's sex; age at diagnosis or reference; maternal attained education; household income in the birth year; maternal age at birth of the index child; maternal tobacco smoking around pregnancy; maternal alcohol consumption; and by *MYCN* oncogene amplification status. *MYCN* oncogene amplification, a marker of aggressive disease and indicator of poor prognosis, was assessed by Southern blot or fluorescent in situ hybridization. Statistical analyses were performed using SAS (version 8.0, Cary, NC). *P*-values are two-sided.

Results

Table 1 presents the demographic characteristics of the 538 cases and 504 controls. Cases and controls were similar with respect to race. Age at diagnosis ranged from 1 day to 17 years, with a mean age of 2.2 (±2.4) years. Cases were 56% male. Case households were significantly more likely to have an annual income below $10,000 or above $50,000. Maternal mean age at birth was 27.5 (±5.5) years and did not differ significantly between cases and controls ($p = 0.15$).

Overall, 88 mothers (8.5%) reported use of any drug during the 10 month period between 1 month prior to pregnancy and childbirth. Of these, 75 (85.2%) used marijuana and 61 (69.3%) used only marijuana and no other

drugs. Cocaine was reported by 15 mothers (19.3%), and seven mothers used both marijuana and cocaine. Only one mother reported heroin use. Drug use data were missing for only four cases and two controls. A total of 11.2% of case mothers and 5.6% of control mothers reported use of any drug from 1 month before pregnancy through childbirth (adjusted OR = 1.82, 95% CI: 1.13, 3.00).

Marijuana was used by mothers of 50 cases (9.3%) and 25 controls (5.0%) in the 10 month window from 1 month prior to conception until the child's birth (adjusted OR = 1.67, 95% CI: 1.00, 2.82). Marijuana use did not differ by race or maternal education. When use of each class of drug was simultaneously adjusted to account for the effect of the other drugs, the risk estimates were attenuated (Table 2). When excluding the month before conception, marijuana use during pregnancy was reported by 34 cases (6.4%) and nine controls (1.8%); (OR = 2.51, 95% CI: 1.18, 5.83, adjusted for use of other drugs during pregnancy). Assigning mothers who never used any drugs to the referent group did not meaningfully change any effect estimate.

Table 3 displays the odds ratios for maternal marijuana use in each time segment around pregnancy and after childbirth, adjusted for use in every other segment. The time period with the strongest association with neuroblastoma was the first trimester (adjusted OR = 4.75, 95% CI: 1.55, 16.48). By contrast, neither use in the month before conception nor use after birth was associated with an increased risk (adjusted OR = 0.89, 95% CI: 0.42, 1.86;

Table 1 Characteristics of children with neuroblastoma diagnosed between birth and age 19 and age-matched controls

	Cases		Controls		Total	Crude OR (95% CI)
	No.	%	No.	%	No.	
Race						
White non-Hispanic	429	79.7	396	78.6	825	1.00
Black	42	7.8	39	7.7	81	0.99 (0.63, 1.57)
Hispanic	49	9.1	54	10.7	193	0.84 (0.56, 1.26)
Other	18	3.4	15	3.0	33	1.11 (0.55, 2.23)
Maternal education						
Less than high school	60	11.2	51	10.1	111	1.42 (0.90, 2.22)
High school graduate	366	68.0	318	63.1	684	1.39 (1.04, 1.86)
College graduate or beyond	112	20.8	135	26.8	247	1.00
Maternal age at birth of child						
<20 years	48	8.9	35	6.9	83	1.33 (0.83, 2.14)
20–24 years	119	22.1	110	21.8	229	1.05 (0.76, 1.45)
25–30 years	212	39.4	206	40.9	418	1.00
31–39 years	148	27.5	146	29.0	294	0.99 (0.73, 1.33)
40–44 years	11	2.0	7	1.4	18	1.53 (0.58, 4.02
Household income, birth year[a]						
<$10,000	89	17.5	54	11.1	143	2.16 (1.39, 3.35)
$10,000–20,000	92	18.1	91	18.7	183	1.32 (0.89, 1.98)
$21,000–30,000	87	17.1	114	23.5	201	1.00
$31,000–40,000	79	15.6	86	17.7	165	1.20 (0.80, 1.82)
$41,000–50,000	54	10.6	52	10.7	106	1.36 (0.85, 2.18)
>$50,000	107	21.1	89	18.3	196	1.58 (1.06, 2.34)

[a] Forty-eight missing (30 cases, 18 controls)

Table 2 Number of cases and controls, odds ratios (OR) and 95% confidence intervals (CI) by maternal use of recreational drugs between one month before pregnancy and childbirth in mothers of children with neuroblastoma and controls

	Cases		Controls		OR (95% CI)[a]	OR (95% CI)[b] adjusted for other drugs used
	No.	%	No.	%		
Any drug						
Never[c]	456	88.4	450	94.1	1.00	
Ever	60	11.6	28	5.9	1.82 (1.13, 3.00)	
Marijuana						
None[d]	484	90.6	477	95.0	1.00	1.00
Any	50	9.4	25	5.0	1.67 (1.00, 2.82)	1.37 (0.77, 2.49)
Cocaine or crack						
None[d]	512	97.9	488	99.2	1.00	1.00
Any	11	2.1	4	0.8	2.59 (0.86, 9.54)	2.09 (0.65, 7.99)
Heroin						
None[d]	534	99.8	502	100	1.00	1.00
Any	1	0.2	0	0	[e]	[e]
Hallucinogens						
None[d]	525	98.9	498	99.8	1.00	1.00
Any	6	1.1	1	0.2	3.39 (0.53, 65.82)	1.48 (0.17, 31.24)
Stimulants						
None[d]	524	98.9	493	99.6	1.00	1.00
Any	6	1.1	2	0.4	2.31 (0.51, 16.10)	1.46 (0.26, 11.01)

[a] Adjusted for household income in the year of birth and age at diagnosis in three categories

[b] Adjusted for use of other drugs during the 10 month time interval and for household income in the year of birth and age at diagnosis in three categories

[c] The referent category includes mothers who never reported any drug in any time interval

[d] The referent category includes mother who never used this drug in any time interval

[e] Unable to calculate

adjusted OR = 0.70, 95% CI: 0.36,1.37, respectively). As evidenced by the wide confidence intervals for these results, the odds ratios for use at any specific time segment around pregnancy were imprecise. Most marijuana use was limited to the month prior to conception and/or first trimester only. Of the 68 case and control mothers who used marijuana in the month before conception, 50 quit before the third trimester. However, 10 regular users smoked marijuana in the month prior to conception and all three trimesters, two of whom reported an average of two pipefuls per day in every time interval. Most mothers were infrequent (< 1/day) users: 57 of 75 women who used marijuana during the 10 month interval of interest always used less than one pipeful per day in each time segment.

Intensity of marijuana use was assessed by assigning the number of pipefuls smoked daily in the first trimester. The offspring of women who smoked less than one pipeful per day had a similar risk to those who used marijuana one or more times per day (adjusted OR = 4.16, 95% CI: 1.52, 14.61; adjusted OR = 4.42, 95% CI: 1.09, 29.58, respectively). Subgroup analyses of cases by *MYCN* oncogene amplification status did not reveal a differential effect of marijuana. Analysis by age at diagnosis revealed a stronger but very imprecise association of maternal marijuana use during pregnancy among children with a diagnosis reference age of less than 1 year of age (OR = 15.61, 95% CI:

3.07, 285.89). The estimate is based on 20 exposed cases and one exposed control and is adjusted for use of other drugs during pregnancy. Effects of maternal marijuana were similar among boys and girls and did not differ by maternal smoking or alcohol use.

Many fewer mothers acknowledged use of other recreational drugs. A total of 11 case mothers and four control mothers reported use of cocaine in the 10 months around pregnancy. The minimum cocaine use was one time only and the maximum was twice a day for 4 months. The mean total number of uses across the 10 month window was 50 (±82). Use in this time window was associated with a suggestion of increased risk (adjusted OR = 2.09, 95% CI: 0.65, 7.9, adjusted for use of other drugs). Use of both marijuana and cocaine did not convey an excess risk beyond the effect of each exposure separately. Heroin, hallucinogens and stimulants were reported by very few mothers, and risk could not be estimated by time segment around pregnancy.

Discussion

Our results suggest that maternal use of marijuana around the time of pregnancy, particularly in the first trimester, is associated with increased risk of neuroblastoma in

offspring. These results differ from a recent Children's Cancer Group study of childhood acute myeloid leukemia (AML), which suggested a decreased risk from maternal marijuana use and no association with paternal marijuana use prior to or during pregnancy [15]. However, our findings further expand previous investigations of parental marijuana use in the prenatal period as a potential risk factor for other childhood cancers. Robison et al. [2] found an increased, but imprecise, risk of acute non-lympho-blastic leukemia (ANLL) among children whose mothers used marijuana and other mind-altering substances prior to or during pregnancy (RR = 11.0, 95% CI: 1.4, 85.2). Ku-itjen et al. [4] identified an elevated risk of astrocytoma with maternal use of marijuana between 1 month prior to conception and childbirth (OR = 2.8, approximate 95% CI: 0.9, 9.9). There was an increased risk of rhabdomyosar-coma with maternal use of marijuana (OR = 3.0, 95% CI: 1.4, 6.5) or cocaine (OR = 5.1, 95% CI: 1.0, 25.0) in the 12 months before birth [5]. A large study of acute lym-phoblastic leukemia (ALL) revealed increased risks asso-ciated with maternal (OR = 1.5, 99% CI: 1.0, 2.1), paternal (OR = 1.3, 99% CI: 1.0, 1.8), or both parents' (OR = 1.8, 99% CI: 1.1, 3.0) use of mind-altering drugs, of which marijuana was predominant [3]. Most studies of marijuana and childhood cancer were not designed to identify a specific time segment of greatest risk.

Weeks 3 through 8 after conception, during the first trimester of pregnancy, are a critical period for organ development and vulnerability to teratogens [16]. How-ever, animal experiments suggest that the nervous system may be more sensitive to chemical carcinogens near the end of gestation [17, 18]. Studies of marijuana toxicology

have explored the plausibility of a carcinogenic process in drug users or their offspring. Smoke generated by a smoking machine system contained 50% higher levels of the polycyclic aromatic hydrocarbons naphthalene, benz[a]anthracene, and benzo[a]pyrene in marijuana cig-arettes than standard tobacco cigarettes [19]. Animal and human data have indicated chromosome damage, as mea-sured by more frequent hypoxanthine phosphoribosyl-transferase (hprt) gene mutations in cord blood of infants born to mothers who smoked marijuana than non-smokers [20]. The active ingredient of marijuana, Δ-9-tetrahydro-cannabinol (THC), and its metabolites cross the placenta and accumulate in the developing embryo [21, 22], with the highest concentrations detected in the fetal central nervous system [23]. Oral Δ-9-THC or inhaled marijuana cigarettes were associated with reduced litter size in mice and rats [22, 24, 25], however, animal pups have not been followed to adulthood to assess tumor development as juveniles or adults, and route and dosage of drug has varied between studies [26].

Our study results indicate a risk of neuroblastoma associated with marijuana smoking around conception and during pregnancy. The 1.8% of control mothers who used marijuana during pregnancy was concordant with estimates from a prevalence study using the National Household Survey on Drug Abuse, which found a 1.8% current use rate in pregnant women [27]. However, measurement error may have been introduced in our study by the use of self-reported substance use without biomarker validation. The primary methodological concern in using self-reported estimates of past exposures is bias due to differential misclassification (recall bias). Parents of cases may recall and report exposures more fully than parents of controls, seeking explanations for a child's illness, or may under-report socially stigmatized behaviors. Parents of controls are thought to have comparatively less motivation to report stigmatized behaviors, according to the social desirability hypothesis [28]. They may also fail to identify truly unexposed time intervals, lacking an incentive to carefully remember exposure dates around pregnancy.

Studies of illicit substance reporting accuracy have no-ted better results in low than high prevalence settings, using a bioassay as the gold standard, and have noted that self-report of marijuana was more accurate than more highly stigmatized drugs [28]. Whether mothers of cases and controls exhibit a differential sensitivity and specificity in self-reporting prenatal drug use has not been established [15]. A sensitivity analysis was performed to assess the likely effect of misclassification of self-reported drug use in a recent study evaluating parental marijuana use and childhood AML etiology. Estimates of self-reporting sen-sitivity and specificity were derived from published studies comparing self-reported drug use in pregnancy with

Table 3 Maternal use of marijuana by time interval around pregnancy, mothers of children with neuroblastoma and controls

	Cases		Controls		Crude OR (95% CI)[a]
	No.	%	No.	%	
Month before pregnancy					
No use	490	91.8	478	95.2	1.00
Any use	44	8.2	24	4.8	0.89 (0.42, 1.86)
First trimester					
No use	505	94.4	496	98.8	1.00
Any use	30	5.6	6	1.2	4.75 (1.55, 16.48)
Second trimester					
No use	522	97.8	498	99.2	1.00
Any use	12	2.3	4	0.8	1.38 (0.22, 9.65)
Third trimester					
No use	521	97.6	498	99.4	1.00
Any use	13	2.4	3	0.6	1.45 (0.23, 10.16)
Birth until diagnosis or reference date					
No use	489	91.7	473	94.2	1.00
Any use	44	8.3	29	5.8	0.70 (0.36, 1.37)

[a] Adjusted for marijuana use at each other time interval around pregnancy, and for household income in birth year and age at diag-nosis in three categories

biologic sampling. Application of these estimates and assumptions about case and control recall bias increased the odds ratios for parental marijuana use and AML [15]. Among those who reported use, there is also concern about underreporting the frequency of use. Fewer than 10% of women who used marijuana during the 10 month window around pregnancy reported using more than one pipeful per day within any time segment. Because of a lack of variability in exposure level per day, we were unable to evaluate a dose response.

Although this is the largest study of risk factors for neuroblastoma yet conducted, some of our results are imprecise due to the small number of mothers reporting drug use around pregnancy. In addition, because of the lower response for fathers of cases and controls we did not have sufficiently thorough self-reported data on paternal drug use. Nonetheless, using the available data on marijuana use by both parents, use by fathers was correlated with use by mothers. The odds ratio for paternal marijuana use around pregnancy was 1.97 (95% CI: 1.24, 3.20), adjusted for age at diagnosis and income. Adding paternal use to multivariate models did not alter the effect of maternal marijuana use.

Correlations between marijuana and tobacco, alcohol, and ''hard'' drugs are of frequent concern in studies of cancer etiology [29]. However, the lack of association between tobacco and alcohol use and the risk of neuroblastoma in our study population suggests an absence of confounding by these exposures. Our study results may also be limited by residual confounding if maternal marijuana use serves as a surrogate for another unmeasured exposure or behavioral factor in neuroblastoma etiology. In addition, the chemical formulation of drugs used by each mother may differ widely, adding to exposure misclassification and rendering comparison of doses.

This is the first study to investigate the association between specific recreational drugs and neuroblastoma within distinct time segments around pregnancy. Our findings indicate that the strongest effect of maternal marijuana use is seen with exposure in the first trimester and among children diagnosed before age one. Given the unfolding understanding of the divergent molecular and clinical patterns of neuroblastoma, there will be great potential for further evaluation of marijuana exposure in association with molecular markers. While previous studies of childhood cancer have suggested an association with marijuana and illicit drugs, additional confirmation is needed.

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